INCREASED SERUM CALCITONIN IN PREGNANCY

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Calcitonin, the hypocalcemic, hypophosphatemic polypeptide hormone of C cell origin, has been reported to be high in pregnant women at delivery. Levels of this hormone were determined by radioimmunoassay in 56 pregnant women in all trimesters and found to be above normal in 72 percent. Values were also increased during the first two days postpartum. Calcitonin levels were not correlated with serum calcium or phosphate, except in the first trimester when levels of this hormone were inversely correlated with serum phosphate. Perhaps the hypercalcitonemia of pregnancy serves to protect the maternal skeleton, while allowing the fetus to accumulate calcium.

It has been reported that pregnant women have a high incidence of hypercalcitonemia at delivery.[1] The authors have studied women during pregnancy and in the postpartum period in order to determine their serum immunoreactive calcitonin (iCT) levels, and to elucidate any possible correlation with serum calcium or phosphate.

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METHODS

Blood was obtained from 56 pregnant women who were attending the prenatal clinic at Howard University Medical Center or who were admitted for therapeutic first-trimester abortions. Additionally, blood was obtained on the second day postpartum from 29 women who were hospitalized at George Washington University Hospital. To obtain normal control values, blood was obtained at known periods of the menstrual cycle from 44 nonpregnant premenopausal women, who were not taking oral contraceptives.

The radioimmunoassay method for calcitonin has been reported previously.[2] The antibody used in this study (Ab-I) has both midportion and carboxyl terminal recognition.[3] With this antibody, serum levels of calcitonin less than 50 pg/ml were undetectable. The serum total calcium was determined by atomic absorption spectroscopy,[4] the serum ionic calcium by a specific ion flow-through method,[5] and serum phosphate by the method of Fiske and Subbarow.[6]

RESULTS

The mean ± significant difference (SD) of serum calcitonin (iCT), calcium, and phosphate levels of normal control women, the pregnant subjects, and the postpartum patients are tabulated in Table 1. Statistical analysis was done by means of

TABLE 1. AGE OF SUBJECTS, SERUM ICT, CALCIUM AND PHOSPHATE

	#	Age, years	iCT (Ab-I) pg/ml ± SD	Calcium Ionic mg/100 ml ± SD	Calcium Total mg/100 ml ± SD	Phosphate mg/100 ml ± SD
Control	44	28 ± 6	103 ± 46	4.84 ± 0.31	9.73 ± 0.37	—
Pregnant						
First Trimester	13	25 ± 4	225 ± 106	4.95 ± 0.05	8.86 ± 0.49	3.60 ± 0.39
Second Trimester	17	25 ± 5	343 ± 181	4.88 ± 0.04	8.82 ± 0.66	3.15 ± 0.48
Third Trimester	19	26 ± 5	306 ± 143	4.85 ± 0.17	8.85 ± 0.57	3.30 ± 0.49
Postpartum	29	22 ± 5	333 ± 150	—	—	—

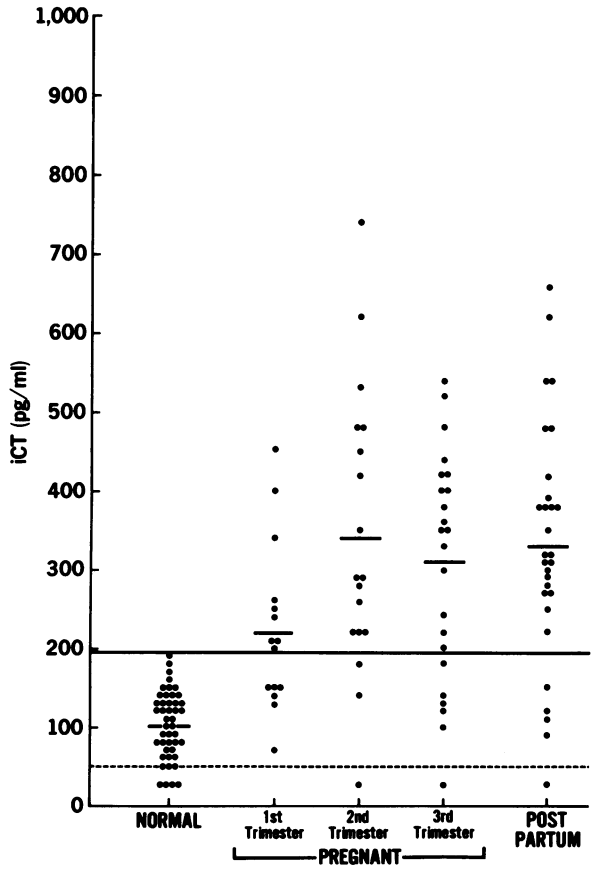

Figure 1. Serum iCT levels in normal, pregnant, and postpartum subjects

Student's t test. No correlation was found between calcitonin levels and stage of the menstrual cycle in normal controls. Figure 1 shows the serum iCT levels of normal control women, women during the three trimesters of pregnancy, and postpartum women. For normal control women, 95 percent of the values were less than 195 pg/ml. The mean iCT level was significantly higher than normal in all trimesters and postpartum ($P<0.001$). The highest mean level, however, was attained during the second trimester, the levels being significantly higher than the first trimester ($P<0.02$). Selecting 200 pg/ml (mean +2 SD) as the upper limit of normal, 72 percent of the pregnant women were hypercalcitonemic. There was no correlation between iCT levels and age or gravida. Also, the serum iCT levels did not correlate with the serum total or ionic calcium or phosphate, except during the first trimester when iCT was inversely correlated with serum phosphate (correlation coefficient: 0.58). In a previous study the authors had found no correlation between iCT and calcium or phosphate in normal controls.[3]

The mean serum iCT level of postpartum women was significantly higher than in nonpregnant women ($P<0.001$), and higher than in women in the first trimester ($P<0.02$).

The total calcium was significantly higher in normal control subjects than in pregnant females; however, there was no significant difference in the ionic calcium between the two groups.

DISCUSSION

Pregnancy

Several investigators have found that serum iCT may be increased during gestation in some animals. Garel et al[7] determined that ewes, ten

days prior to delivery, had high iCT values which decreased after delivery, but increased again during lactation. Garel and Jullienne[8] reported that rats, which were 17.5 days pregnant, had serum iCT levels which exceeded that of virgin rats. These iCT levels, which could be augmented by calcium infusion, increased to a maximum on day 19.5, and returned to near normal levels just prior to delivery (day 21.5).

Konopka et al[9] measured the serum calcitonin of nonpregnant and pregnant women by bioassay and found that 57.4 percent of pregnant women had increased values. The increase during gestation was statistically significant in the second and third trimester. Values in the second and third trimester were similar, but values postpartum were slightly higher. These authors proposed that hypercalcitonemia may serve to protect the skeleton against demineralization during pregnancy. Samaan et al[1] first reported that iCT levels were increased in women at delivery. Pitkin et al[10] found no consistent change in iCT during a longitudinal study of pregnant subjects. Drake et al[11] found a higher mean level of iCT, but no serial change was observed during pregnancy. In agreement with the authors' study, Stevenson et al[12] found elevated iCT levels throughout pregnancy and lactation. The difference in region specificities of the antisera used in the various studies may account for the differences in some of these results.[3]

Pregnancy exerts a profound influence upon calcium metabolism, accompanied as it is by osseous formation in the fetus. The human fetus accumulates 20-30 gm of calcium, mostly in the third trimester.[13] Duggin et al[13] found that women have a positive calcium balance during pregnancy, but considerably less so than the amount estimated to be necessary for the fetus. The increased levels of iCT during gestation suggest that this hormone plays a role in the protection of the maternal skeleton. Indirect evidence for this hypothesis was provided by Lewis and coworkers[14] who reported that thyroidectomized rats which had been kept on replacement thyroxine and whose parathyroid function was maintained by autotransplanted parathyroid glands had, after gestation, femurs which were lighter and contained less calcium and phosphate than controls. Similarly, Barlet and Garel[15] found that thyroidectomy of thyroid-supplemented goats early in pregnancy resulted in decreased mineral content of their bones at the end of gestation, even though the animals were fed a high calcium diet. Interestingly, Reynolds and coworkers[16] have found that the hypocalcemic response to the exogenous administration of calcitonin in pregnant rhesus monkeys was greater than for nonpregnant animals; this fact suggests that gestation might result in augmented sensitivity to endogenous calcitonin. Klotz et al[17] found that estrogen therapy in rats induced hypercalcitonemia. The authors have found that women taking estrogens have higher iCT levels than women not taking estrogen.

It is known that parathyroid hormone (PTH) levels are increased in women during pregnancy and lactation.[10,18] Pitkin et al[10] suggested that a physiologic hyperparathyroidism exists during pregnancy. In this regard, Heaney and Skillman[19] found that intestinal absorption of calcium doubled in pregnancy, a fact they attributed, in part, to increased PTH. Perhaps the osteolytic activity of PTH is countered by the hypersecretion of calcitonin. This action may permit the calcium-retaining actions of PTH to be exerted on the gut and kidney while the calcium needs of the fetus are met, thus, sparing the maternal skeleton.

It would appear that the hypercalcitonemia of pregnancy is not explicable exclusively on the basis of maternal to fetal calcium transfer or hyperestrogenism. If the high iCT levels measured were the result exclusively of increased mobilization and transport of calcium from the mother to fetus, this hormone would be expected to be at its highest during the third trimester, when the fetus accumulates the bulk of its calcium. However, there was no significant increase in calcitonin from the second to the third trimester. Similarly, estrogen production by the placenta is not likely to be the sole stimulus to calcitonin secretion since placental estrogen increases progressively until delivery.

Some investigators have found a minimal decrease in serum total calcium during pregnancy, which has been attributed to hemodilution or a decrease in serum albumin; others have found a progressive decline, followed by a rise just prior to gestation; still others have found no change.[9,10,20,21] In the authors' study, the mean total calcium was not significantly different during the three trimesters of pregnancy, although the mean total calcium level was significantly lower

than that of normal females. The mean ionic calcium remained normal even though it was insignificantly lower in the second trimester. Drake et al[11] found a decrease in ionic calcium at 21-25 weeks gestation which remained low until term. In the present study, the serum phosphate was less in the second trimester.

Postpartum

Black and Capen[22] showed that parturient cows have high serum iCT levels, and those cows which developed postpartum hypocalcemia and paresis had significantly higher values than the normocalcemic cows. In contrast, Mayer et al[23] did not detect an increase in iCT levels in cows which developed parturient hypocalcemic paresis. In humans, Konopka et al[9] measured serum calcitonin by bioassay, and reported increased values postpartum. The postpartum values were statistically greater than those achieved during pregnancy.

In the present study, elevated iCT levels were documented on the second postpartum day. Stevenson et al[12] found similar results. Calcium requirements are increased during lactation as they are in pregnancy. Perhaps, during lactation as well as in pregnancy, increased serum iCT levels protect the maternal skeleton.

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